

WORLD HEALTH ORGANIZATION  
INTERNATIONAL AGENCY FOR RESEARCH ON CANCER



# IARC MONOGRAPHS ON THE EVALUATION OF CARCINOGENIC RISKS TO HUMANS

## **VOLUME 73** **SOME CHEMICALS THAT CAUSE** **TUMOURS OF THE KIDNEY OR** **URINARY BLADDER IN RODENTS** **AND SOME OTHER SUBSTANCES**

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**IARC MONOGRAPHS**  
**ON THE**  
**EVALUATION OF CARCINOGENIC**  
**RISKS TO HUMANS**

*Some Chemicals that Cause Tumours of the  
Kidney or Urinary Bladder in Rodents  
and Some Other Substances*

**VOLUME 73**

This publication represents the views and expert opinions  
of an IARC Working Group on the  
Evaluation of Carcinogenic Risks to Humans,  
which met in Lyon,

13–20 October 1998

1999

## IARC MONOGRAPHS

In 1969, the International Agency for Research on Cancer (IARC) initiated a programme on the evaluation of the carcinogenic risk of chemicals to humans involving the production of critically evaluated monographs on individual chemicals. The programme was subsequently expanded to include evaluations of carcinogenic risks associated with exposures to complex mixtures, life-style factors and biological agents, as well as those in specific occupations.

The objective of the programme is to elaborate and publish in the form of monographs critical reviews of data on carcinogenicity for agents to which humans are known to be exposed and on specific exposure situations; to evaluate these data in terms of human risk with the help of international working groups of experts in chemical carcinogenesis and related fields; and to indicate where additional research efforts are needed.

The lists of IARC evaluations are regularly updated and are available on Internet: <http://www.iarc.fr/>.

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An evaluation may be made for a group of chemical compounds that have been evaluated by the Working Group. In addition, when supporting data indicate that other, related compounds for which there is no direct evidence of capacity to induce cancer in humans or in animals may also be carcinogenic, a statement describing the rationale for this conclusion is added to the evaluation narrative; an additional evaluation may be made for this broader group of compounds if the strength of the evidence warrants it.

The agent, mixture or exposure circumstance is described according to the wording of one of the following categories, and the designated group is given. The categorization of an agent, mixture or exposure circumstance is a matter of scientific judgement, reflecting the strength of the evidence derived from studies in humans and in experimental animals and from other relevant data.

*Group 1—The agent (mixture) is carcinogenic to humans.*

*The exposure circumstance entails exposures that are carcinogenic to humans.*

This category is used when there is *sufficient evidence* of carcinogenicity in humans. Exceptionally, an agent (mixture) may be placed in this category when evidence of carcinogenicity in humans is less than sufficient but there is *sufficient evidence* of carcinogenicity in experimental animals and strong evidence in exposed humans that the agent (mixture) acts through a relevant mechanism of carcinogenicity.

*Group 2*

This category includes agents, mixtures and exposure circumstances for which, at one extreme, the degree of evidence of carcinogenicity in humans is almost sufficient, as well as those for which, at the other extreme, there are no human data but for which there is evidence of carcinogenicity in experimental animals. Agents, mixtures and exposure circumstances are assigned to either group 2A (probably carcinogenic to humans) or group 2B (possibly carcinogenic to humans) on the basis of epidemiological and experimental evidence of carcinogenicity and other relevant data.

*Group 2A—The agent (mixture) is probably carcinogenic to humans.*

*The exposure circumstance entails exposures that are probably carcinogenic to humans.*

This category is used when there is *limited evidence* of carcinogenicity in humans and *sufficient evidence* of carcinogenicity in experimental animals. In some cases, an agent (mixture) may be classified in this category when there is *inadequate evidence* of carcinogenicity in humans, *sufficient evidence* of carcinogenicity in experimental animals and strong evidence that the carcinogenesis is mediated by a mechanism that also operates in humans. Exceptionally, an agent, mixture or exposure circumstance may be classified in this category solely on the basis of *limited evidence* of carcinogenicity in humans.

*Group 2B—The agent (mixture) is possibly carcinogenic to humans. The exposure circumstance entails exposures that are possibly carcinogenic to humans.*

This category is used for agents, mixtures and exposure circumstances for which there is *limited evidence* of carcinogenicity in humans and less than *sufficient evidence* of carcinogenicity in experimental animals. It may also be used when there is *inadequate evidence* of carcinogenicity in humans but there is *sufficient evidence* of carcinogenicity in experimental animals. In some instances, an agent, mixture or exposure circumstance for which there is *inadequate evidence* of carcinogenicity in humans but *limited evidence* of carcinogenicity in experimental animals together with supporting evidence from other relevant data may be placed in this group.

*Group 3—The agent (mixture or exposure circumstance) is not classifiable as to its carcinogenicity to humans.*

This category is used most commonly for agents, mixtures and exposure circumstances for which the *evidence of carcinogenicity is inadequate* in humans and *inadequate* or *limited* in experimental animals.

Exceptionally, agents (mixtures) for which the *evidence of carcinogenicity is inadequate* in humans but *sufficient* in experimental animals may be placed in this category when there is strong evidence that the mechanism of carcinogenicity in experimental animals does not operate in humans.

Agents, mixtures and exposure circumstances that do not fall into any other group are also placed in this category.

*Group 4—The agent (mixture) is probably not carcinogenic to humans.*

This category is used for agents or mixtures for which there is *evidence suggesting lack of carcinogenicity* in humans and in experimental animals. In some instances, agents or mixtures for which there is *inadequate evidence* of carcinogenicity in humans but *evidence suggesting lack of carcinogenicity* in experimental animals, consistently and strongly supported by a broad range of other relevant data, may be classified in this group.

## References

- Breslow, N.E. & Day, N.E. (1980) *Statistical Methods in Cancer Research*, Vol. 1, *The Analysis of Case-Control Studies* (IARC Scientific Publications No. 32), Lyon, IARC
- Breslow, N.E. & Day, N.E. (1987) *Statistical Methods in Cancer Research*, Vol. 2, *The Design and Analysis of Cohort Studies* (IARC Scientific Publications No. 82), Lyon, IARC
- Cohen, S.M. & Ellwein, L.B. (1990) Cell proliferation in carcinogenesis. *Science*, **249**, 1007–1011
- Gart, J.J., Krewski, D., Lee, P.N., Tarone, R.E. & Wahrendorf, J. (1986) *Statistical Methods in Cancer Research*, Vol. 3, *The Design and Analysis of Long-term Animal Experiments* (IARC Scientific Publications No. 79), Lyon, IARC

In male rats, methyl *tert*-butyl ether-induced kidney lesions were associated with  $\alpha_{2u}$ -globulin nephropathy, a male rat-specific response. Exposure of female mice to 8000 ppm [29 g/m<sup>3</sup>] methyl *tert*-butyl ether in air was mitogenic to the liver and caused changes in oestrogen-regulated tissues.

Methyl *tert*-butyl ether did not induce developmental toxicity in rats or rabbits exposed via inhalation to concentrations that affected maternal food consumption. In one study in mice, increased incidences of postimplantation loss and cleft palate were seen at doses that also induced hypoactivity, ataxia and reduced food consumption in the dams. Another study in mice, conducted at lower doses that were less toxic to dams, did not provide evidence of developmental toxicity.

No data were available on the genetic and related effects of methyl *tert*-butyl ether in humans. The few available data indicate that methyl *tert*-butyl ether is not genotoxic in experimental systems.

### 5.5 Evaluation

There is *inadequate evidence* in humans for the carcinogenicity of methyl *tert*-butyl ether.

There is *limited evidence* in experimental animals for the carcinogenicity of methyl *tert*-butyl ether.

### Overall evaluation

Methyl *tert*-butyl ether is *not classifiable as to its carcinogenicity to humans (Group 3)*.

## 6. References

- Agency for Toxic Substances and Disease Registry (1996) *Toxicological Profile for Methyl tert-Butyl Ether*, Atlanta, GA
- Allen, K.M., Grande, D. & Foley, T. (1996) Monitoring reformulated gasoline in Milwaukee, Wisconsin. In: *A&WMA Conference on the Measurement of Toxic and Related Air Pollutants, Research Triangle Park, NC, May 7–9 1996*, Madison, WI, Wisconsin Department of Natural Resources
- Almaguer, D. (1993) *NIOSH Health Hazard Evaluation Report* (Report No. HETA 93-0884-2344), Cincinnati, OH, National Institute for Occupational Safety and Health
- American Conference of Governmental Industrial Hygienists (1997) *1997 TLVs® and BEIs®*, Cincinnati, OH, p. 29
- American Petroleum Institute (1989) *Monitoring Near Refineries for Airborne Chemicals*, Vol. 1, *Validated Ambient Air Concentrations around Three Refineries* (Publ. No. 4484), Washington DC
- Anon. (1997) MTBE—The quest for cleaner air. *Asian chem. News*, May 12
- Arco Chemical Co. (1993) *Product Safety Bulletin: Methyl Tertiary Butyl Ether*, Newtown Square, PA, Environmental Health and Safety Department